# Formulation and Evaluation of Nanoparticles of Isoniazid-Rifampicin Co-loaded with Bioactive Agent (Curcumin/Piperine) For Improved Management of Tuberculosis

*Synopsis*

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# Formulation and Evaluation of Nanoparticles of Isoniazid-Rifampicin Co-loaded with Bioactive Agent (Curcumin/Piperine) For Improved Management of Tuberculosis

## Introduction

Tuberculosis (TB) is one of the biggest hazards to public health worldwide because of its increased rate of human mortality and morbidity. Prior to the COVID-19 pandemic, TB surpassed HIV/AIDS as the most common contagious agent-related reason for death. The total number of individuals receiving a new diagnosis of TB decreased from 7.2 million in 2019 to 5.7 million in 2020. Additionally, less availability of treatment and diagnosis of TB has directed to a rise in TB-related mortality. Globally speaking, though there might help in lowering the TB load, it is not sufficient to meet the End TB Strategy's initial objective. A further risk to the worldwide control of TB is drug-resistant strains of the disease. In certain parts of the globe, the prevalence of extensively drug-resistant tuberculosis (XDR-TB) and multi-drug-resistant tuberculosis (MDR-TB) is rising. With significant regional variations, 71% (2.2/3.0 million) of patients worldwide with bacteriologically proven respiratory tuberculosis in 2020 underwent testing for rifampicin tolerance. Of them, 25,682 cases of pre-XDR or XDR-TB and 131,222 cases of MDR-TB were found (WHO, 2021). Drug susceptibility testing (DST) techniques need to be precise and repeatable due to the rise in drug-resistant tuberculosis cases. The World Health Organization (WHO) suggested changing the focus of the TB policy from halt elimination in 2015. (WHO, 2022). In order to do this, the WHO has highlighted how crucial it is to identify *Mycobacterium tuberculosis* (*M.tb*) as early as possible and precisely, and to determine whether a drug is susceptible to it while treating the disease. The state-of-the-art diagnostic approaches that not only concentrate on *M.tb* identification but also identify *M.tb* -specific host response and novel methodologies for tuberculosis diagnosis.

## Literature Review

The main issue with the present chemotherapy for tuberculosis is many compounds within the drug, whether given intravenously or orally, are not able to penetrate their intended site and remain in the body, leading to harmful side effects. This distribution of the drug across the body occurs via systemic circulatory system. The short plasma-life and quick elimination of drugs restrict their efficacy. Long periods of treatment and common, continual dosage of various medications are the main issues with the treatment, they cause patients to comply poorly or not at all with present therapy. The primary cause of the disease's recurrence and the establishment of both extensively drug-resistant (XDR) tuberculosis and multidrug-resistant (MDR) tuberculosis, the more severe form of the illness (MDR-TB and XDR-TB). That constituted a serious issue and an obstacle to the fields of medicine. Also, AIDS plays a significant role in the rising prevalence of tuberculosis by creating an environment that is conducive to the growth of *M.tb* in a host with compromised immunity .To address the issue of drug resistance, reduce the time of therapy, and improve compliance, novel and efficient anti-TB medications must be developed in light of the alarming rise of MDR and XDR strains and the dearth of viable treatment choices.

Drug carriers are made of nanoparticles that are submicron (1μm) particles with colloidal structure. Drugs can be either integrated into the particle structure or covalently fixed to the particle surface for medicinal purposes. Biocompatible and biodegradable substances, including polymers—which may be natural, like albumin and gelatin—or synthetic, like polylactides and polyalkylcyanoacrylates—or solid lipids, like SLN and NLC—type nanoparticles. Because they are absorbed by cells more quickly than larger molecules, nanoparticles provide a promising means of distribution and transportation.

## Rationale and Justification

Nanoparticles (NPs) are ultra-small carriers (typically 1–100 nm) engineered to encapsulate pharmaceuticals, altering their distribution, release, and cellular uptake. In TB treatment, these carriers offer several advantages over traditional formulations. First, NPs can provide controlled and sustained drug release, maintaining therapeutic drug concentrations over extended periods and potentially reducing dosing frequency. Nanoparticles can be functionalized with targeting ligands, such as mannose or other receptor-specific groups, to enhance uptake by macrophages—the very cells that harbor TB bacteria. For instance, mannose-decorated lipid-polysaccharide nanoparticles loaded with RIF and INH demonstrated improved internalization and higher intracellular drug accumulation compared to non-targeted counterparts, underscoring their potential to increase therapeutic effect at the site of infection. Co-encapsulation of RIF and INH within the same nanoparticle system offers important therapeutic synergies. This strategy ensures that both drugs are delivered simultaneously to the infected site, preserving their synergistic antimicrobial action while reducing the potential for undesirable chemical interactions and degradation that occur when the drugs are orally co-administered in free form. Moreover, nanocarriers such as polymeric systems and mesoporous silica nanoparticles have been shown to increase the intracellular concentrations of both drugs, thereby improving bactericidal activity and reducing the minimum inhibitory concentration relative to free drugs. The pharmacokinetic profiles of rifampicin and isoniazid are inherently limited in conventional forms due to rapid clearance and metabolic variability, particularly for INH, which is heavily metabolized via acetylation pathways leading to dose-dependent hepatotoxicity in some individuals. Nanoparticle encapsulation can normalize exposure by modulating drug release kinetics and reducing peak systemic concentrations, thereby lowering systemic toxicity and improving patient safety profiles. Additionally, sustained release systems may improve patient adherence by decreasing dosing frequency, critical for TB regimens that require long durations of therapy. TB therapy is increasingly complicated by the emergence of drug-resistant strains and protective biofilms formed by *M. tuberculosis*. By locally concentrating drugs where needed most, nanoparticles may reduce the selection pressure for resistant mutants and provide sustained attack against persistent bacilli. In conclusion, the integration of nanoparticles for co-delivery of rifampicin and isoniazid represents a transformative advancement in TB pharmacotherapy. By improving targeted delivery, enhancing pharmacokinetics, enabling controlled release, and reducing systemic toxicity, nanoparticle-based systems can significantly overcome the limitations of conventional regimens. These advances also hold potential to improve patient adherence, combat drug resistance, and ultimately contribute to more effective TB control worldwide. Continued research and clinical translation efforts are critical to realize the full potential of nanotechnology in combating this global health threat.

## Objectives

- To design and develop polymeric nanoparticulate formulations co-encapsulating isoniazid and rifampicin along with curcumin and piperine by nanoprecipitation technique.
- To optimize formulation and process variables using a Design of Experiments (DOE) approach to obtain nanoparticles with desired physicochemical characteristics.
- To assess the antimicrobial activity of the developed formulations by determining the minimum inhibitory concentration (MIC) against *M.tb*.
- To evaluate cytotoxicity of the optimized formulations using appropriate cell line models.

- To study *ex vivo* survival and intracellular uptake of the nanoparticulate systems in biological environments relevant to tuberculosis infection.

**Methodology**

- Preformulation studies
- Characterization of the drug (IR spectroscopy, UV spectrophotometery and DSC, etc.)
- Preparation and Optimization of Isoniazid-Rifampicin loaded Nanoparticles
- Preparation of Bioactive (Curcumin, Piperine) loaded Isoniazid-Rifampicin Nanoparticles
- Characterization of prepared Nanoparticles (Size, Zeta potential, TEM, Entrapment efficiency)
- *In vitro* drug release
- Cytotoxicity assay
- Stability studies

**Expected Outcomes**

- Bioactive compounds (Curcumin, Allicin, Glabridin, Piperine) act as an adjunct to classical antibiotics and hold great promise for the treatment of drug-sensitive as well as drug-resistant TB.
- Slow and sustained release of drugs from nanoparticles can be desired, unlike the conventional oral formulations which result in systemic toxicity.
- Developed system can improve bioavailability, solubility, permeability, and site-specific targeting to minimize the prevalence of MDR-TB.
- Combinaton based therapy could offer a potential advantage over conventional therapy for TB, which has a great potential to diminish the drug regimen and would be able to make better predictions about the future trajectory of the disease by the data, as the ministry has been focusing on the goal of ending TB by 2025.

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**Signature of the Scholar**

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